AMENDMENT

In the Claims:

Please cancel Claims 2-7 and 18.

Please amend the Claims as follows:

8. **(Amended)** A pharmaceutical composition comprising a recombinant adeno-associated virus (AAV) virion comprising a nucleotide sequence encoding a functional Factor VIII protein, wherein said recombinant adeno-associated virus virion lacks AAV *rep* and *cap* genes.

9. **(Amended)** The pharmaceutical composition of Claim 8, wherein said nucleotide sequence encoding a functional Factor VIII protein is operably linked to a tissue-specific promoter.

In the Specification:

Please substitute the Title with "Adeno-Associated Virus Vector Compositions for Expression of Factor VIII."

REMARKS

Applicants wish to thank the Examiner for the telephone interview on March 19, 2002 and helpful comments provided therein. At the interview, general agreement was reached concerning the patentably of the presently amended claims over the references of record.

Claims 2-7 and 18 have been canceled and Claims 8 and 9 have been amended. Claims 8-17 and 19 are now pending. The changes made to the claims by the current amendment, including [deletions] and additions, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this Preliminary Amendment. Support for the above amendments can be found throughout the specification, e.g., at p. 4, lines 24-27, p. 9, lines 10-12, p. 19, lines 18-24 and p. 23, lines 15-22.

The amendment and cancellation are without prejudice, without any intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing application hereof containing the original claims.

Double Patenting Rejection

The Office rejected Claims 8-15 and 19 under the judicially created doctrine of obviousness-type double patenting over Claims 1, 5, and 11-13 of U.S. Patent No. 6,200,560 or Claims 1, 5, and 11-13 of U.S. Patent No. 6,221,349. These rejections are believed to be overcome for reasons discussed below.

In particular, applicants are submitting a Terminal Disclaimer, disclaiming the terminal portion of any patent granted on the above-captioned application that would extend beyond the expiration dates of U.S. Patent Nos. 6,200,560 and 6,221,349. Accordingly, the obviousness-type double patenting rejection over these patents is overcome.

Rejection Under 35 U.S.C. § 103(a):

Claims 8-17 and 19 were examined in the Office Action dated January 17, 2002 and rejected under 35 U.S.C. § 103(a) as being unpatentable over Chiorini et al. when taken in view of Simonet. Specifically, the Office contends "Chiorini teaches an AAV vector and AAV particles generated therefrom. ... Chiorini further teaches that the DNA sequence may encode Factor VIII and be under control of a suitable promoter." Office Action, page 6. Further, the Office indicates that "at the time the invention was made, tissue specific promoters, specifically liver specific promoters (e.g. TTR) were well known in the art for use in enhancing liver expression of a transgene using a vector as exemplified by Simonet."

Applicants traverse the rejection and supporting remarks.

The Cited Art Does Not Provide a Reasonable Expectation of Success

In the present case, the cited references do not establish a *prima facie* case of obviousness most notably because the primary reference (Chiorini) would not provide a

reasonable expectation of success for achieving the claimed invention. Such a reasonable expectation of success is required to make a proper *prima facie* showing of obviousness. (See, e.g., Amgen v. Chugai, 18 USPQ2d 1016 (Fed. Cir. 1991)). Here, no reasonable expectation of success could have been had because (1) the cited references do not even remotely enable the claimed compositions, and (2) the art as a whole taught away from the claimed compositions at the time of filing.

In his Office Action, the Examiner notes "Chiorini ... teaches that the DNA sequence may encode Factor VIII and be under control of a suitable promoter (column 3, lines 5-30)." However, in order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method. Motorola Inc. v. Interdigital Tech. Corp. (Fed. Cir. 1997). In this case, aside from the blanket statement that the DNA sequence *may* encode Factor VIII, Chiorini provides absolutely no enabling disclosure for achieving the claimed compositions.

Significantly, at the time of filing, the art widely recognized that Factor VIII *could not* be packaged into rAAV. Even after applicants' priority date, Hortelano and Chang (cited by the Examiner) acknowledged:

> Despite the promising results obtained with AAV vectors delivering hFIX, it has not yet been used to deliver FVIII. The genome of AAV is only 4.7 kb, too short to harbour the full-size hFVIII cDNA (7 kb). Even the truncated version of hFVIII (4.4 kb) obtained after removing the B domain is larger than the maximum genetic sequences that can be accommodated, highlighting the greater technical difficulty in expressing FVIII.

Although Chao et al. (Blood 2000, 95: 1594-1599) packaged B-domain-deleted Factor VIII in AAV after applicants' priority date, they indicated that prior to their findings this was not thought possible: "[because] B-domain-deleted hFVIII cDNA (BDD-hFVIII) is 4.4 kb [it was] not thought feasible for testing in rAAV." See also, Gnatenko et al. (Brit. J. Haematology 1999, 104: 27-36) asserting that their data "provide the first evidence that rAAV is an adaptable virus for FVIII delivery."

In this case, Chiorini provides no guidance whatsoever for overcoming AAV's widely known packaging limitation in order to package the Factor VIII gene in rAAV. Although B-domain-deleted constructs of Factor VIII were generally known at the time of filing, as demonstrated above, it was widely believed that such constructs could not be

packaged and expressed using rAAV. Therefore, at least three references published *after* applicants filing date demonstrate that Chiorini et al. is not enabling and further demonstrate that the presently claimed compositions are novel.

In making an obviousness rejection, the Examiner must consider the state of the prior art as a whole. In doing so in the present case, it is clear that the closest art at the time of filing taught away from the claimed invention. "In general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." In re Gurley, 27 F.3d 551, 553. As discussed above, at least three references published after applicants filing date indicate that FVIII could not be packaged in rAAV. Applicants are not aware of any other art at the time of filing that alone, or in combination, taught otherwise.

CONCLUSION

Applicants respectfully submit that the present claims are patentable. If the Examiner notes any further matters which he believes may be resolved by a telephone interview, he is encouraged to contact Kenneth G. Chahine by telephone at (510) 748-7154 or by fax at (510) 748-7155.

Respectfully submitted,

Date: 17 Apr. 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend the Claims as follows:

8. **(Amended)** A pharmaceutical composition comprising a recombinant adeno-associated virus (AAV) virion comprising a nucleotide sequence encoding **[at least one]**a functional Factor VIII **[subunit, operably linked to a tissue-specific promoter]** protein, wherein said recombinant adeno-associated virus virion lacks AAV *rep* and *cap* genes.

9. **(Amended)** The pharmaceutical composition of Claim 8, wherein said nucleotide sequence encoding a functional Factor VIII protein is operably linked to a tissue-specific promoter.